REMARKS/ARGUMENTS

These Remarks are responsive to the Office Action mailed March 18, 2005 ("Office Action"). Claims 1, 5-6, 9-14, 16-18, 29-31, 35-36, 39, and 42 are pending in the application. The specification has been amended to add missing trademark symbols to Tables 3.1 and 3.2. Applicant respectfully requests reconsideration of the rejection of the pending claims for the following reasons.

Statement of Substance of the Interview

On June 7, 2005, Examiner Steadman extended Applicant the courtesy of an interview. Applicant would like to thank Examiner Steadman for agreeing to an interview. During the interview, all grounds of rejection were discussed, which include the rejection of:

(a) claims 6, 9-12, and 35-36 under 35 U.S.C. § 112, second paragraph, for indefiniteness;

(b) claims 1, 5-6, 9-14, 16-18, 29-31, 35-36, 39, and 42-43 under 35 U.S.C. § 112, first paragraph, for lack of written description;

(c) claims 1, 5-6, 9-14, 16-18, 29-31, 35-36, 39, and 42-43 under 35 U.S.C. § 112, first paragraph, for lack of enablement; and

(d) claims 1, 5-6, 9, 12-14, 16-18, 29-31, 35-36, and 42-43 under 35 U.S.C. § 103 as being unpatentable over Ward et al., Biotechnol 8:435-440 ("Ward") in view of WO 95/29999 ("Larsen").

During the interview, Examiner Steadman stated that the independent claim 1 would be viewed more favorably than dependent claims 6, 9-12, and 35-36 with respect to the description/scope of enablement rejections. In response to questions from Applicant's representative during the interview about the use of the term "best mode" in the Office Action (e.g., at page 11 of the Office Action), Examiner Steadman clarified that he was not using the term in the sense of "failure to disclose the best mode," but was referring to the desirability of pursing products in the prior art with glucoamylase activity.

Specification/Objection

The Office Action objects to the specification in the use of the trademarks Hannilase™, Thermolase™, and Modilase™. The Office Action states that "applicants have failed to amend the specification to capitalize the disclosed trademarks." Office Action, page 2. Applicants have reviewed the specification and found that the term "Thermolase" in tables 3.1 and 3.2 did not have a trademark symbol attached. Applicant did not find any instance where a trademark term was set forth in lower case. Therefore, Applicant respectfully requests that the Examiner point out specifically where the trademark term is used improperly in the specification.

Indefiniteness -- 35 U.S.C. § 112, 2d para.

The Office Action rejects claims 6, 9-12, and 35-36 under 35 U.S.C. § 112, second paragraph, for indefiniteness.

The legally correct standard for determining whether a claim is indefinite under 35 U.S.C. § 112, second paragraph, requires a determination of whether a person of ordinary skill in the art would understand what is claimed. "A decision on whether a claim is invalid under § 112, 2d para., requires a determination of whether those skilled in the art would understand what is claimed when the claim is read in light of the specification." Orthokinetics, Inc. v. Safety Travel Chairs, Inc., 806 F.2d 1565, 1 U.S.P.Q.2d 1081 (Fed. Cir. 1986). The Office Action has concluded that the claims are indefinite, but has made no showing that a person of ordinary skill in the art cannot understand what is claimed. Accordingly, the rejection for indefiniteness is improper and must be withdrawn.

The Office Action alleges that the claims omit essential steps in the sense that they are not limited to "the alteration of an organism that does not endogenously express chymosin and/or glucoamylase. . . ." Office Action, page 4. The Office Action enumerates a number of specific genera and species and concludes that "[i]n the absence of endogenous expression of a polypeptide having chymosin and/or glucoamylase activities in these organisms, it is unclear as to how such activities are present in the medium derived from their cultivation." Office Action, pp. 4-5. However, the specification teaches numerous commercial rennets having glucoamylase (GAM) activity, see Table 3.1, page 15, as well as a recombinant *Aspergillus niger* var. *awamori*

in Examples 1 and 2 that have GAM activity. See Fig. 1 and its corresponding description at page 9 of the specification. Furthermore, the specification clearly teaches that the problem of undesired enzymatic activities or side activities is not limited to peptide products of recombinant organisms and can include "milk clotting enzymes of both animal and microbial origin . . . produced using either organisms naturally producing such an enzyme or using recombinant host microorganisms having an inserted gene expressing the milk clotting enzyme." Specification, page 5. Based on the foregoing, there is simply no support for the proposition that the specification has described "the alteration of an organism that does not endogenously express chymosin and/or glucoamylase" as an essential step. Accordingly, the rejection of claims 6, 9-12, and 35-36 under 35 U.S.C. § 112, second paragraph, for indefiniteness must be withdrawn.

Written Description -- 35 U.S.C. § 112, first paragraph

The Office Action rejects claims 1, 5-6, 9-14, 16-18, 29-31, 35-36, 39, and 42-43 under 35 U.S.C. § 112, first paragraph, for lack of written description.

"The examiner has the initial burden of presenting by a preponderance of evidence why a person skilled in the art would not recognize in an applicant's disclosure a description of the invention defined by the claims." M.P.E.P. § 2163.04 (citing In re Wertheim, 541 F.2d 257, 263, 191 USPQ 90, 97).

The rationale of the Office Action for concluding that the claims lack written description appears to be based on an alleged lack of written description support for the materials provided in step (i) of the claims. Step (i) of claim 1 requires "providing a medium having a pH of 2.0 or higher that comprises chymosin activity and glucoamylase activity." The Office Action refers to the medium produced by culture of *Aspergillus niger* var. *awamori* expressing a recombinant bovine pro-chymosin-glucoamylase fusion protein and then states "[o]ther than this single working example of the genus of recited media, the specification fails to disclose any other species of a medium that comprises chymosin activity and glucoamylase activity." Office Action, page 7. Applicant respectfully disagrees. In addition to Examples 1-2, the specification sets forth Example 3 which discloses microbial and animal rennet products having both chymosin and glucoamylase activity. These commercially available products disclosed in Example 3 include:

> Hannilase™ 195 (a microbial coagulant produced by *Rhizomucor miehei*), Hannilase™ 2100 (a bovine chymosin produced by *Aspergillus niger* var. *awamori*), CHY-MAX™ (a bovine chymosin produced by *Aspergillus niger* var. *awamori*), Modilase™ (an oxidized, thermolabile coagulant derived from *Rhizomucor meihei*), and Thermolase™ (a microbial coagulant produced by *Cryphonectria parasitica*).

Furthermore, the specification makes clear that numerous ways are available for making a medium having chymosin activity and glucoamylase activity. For instance, the specification states the following at page 2:

> Milk clotting enzymes of microbial origin are currently in commercial use in the diary industry. In the following, such enzymes are also referred to as microbial clotting enzymes, microbial rennets or microbial coagulants. Examples of such enzymes include aspartic proteases natively produced by the filamentous fungal species *Rhizomucor miehei* and *Rhizomucor pusillus* and protease naturally produced by the fungal species *Cryphonectria parasitica*. Enzymes having milk clotting activity are also produced naturally by other fungal species including *Rhizopus* species, *Physarium* species and *Penicillium* species, and *Bacillus* species.

The specification also describes media that can be treated according to the present invention on pages 6-7:

> It will be appreciated that any starting material or intermediate material that is applied in the manufacturing of a preparation containing a desired polypeptide as well as the final product as such can be subjected to the treatment at low pH. Typical examples of such materials that are treated in accordance with the invention include media derived from the cultivation of a microorganism that during its cultivation produces at least one desired polypeptide and at least one undesired enzymatic side activity as defined herein. In accordance with the invention such media to be treated include media derived from cultivation of animal cells, plant cells and microbial cells including cells of a bacterial species such as a gram negative bacterial species including *E. coli* and a gram positive species including a *Bacillus* species, a yeast species and a species of filamentous fungi. Thus, media which can be treated by the method of the invention include media derived from the cultivation of cells of a yeast species selected from *Saccharomyces cerevisiae*, a methylotrophic yeast species including *Pichia pastoris* and a *Klyuveromyces* species, and media from cultivation of species of filamentous fungi such as e.g. *Aspergillus* species, *Cryphonectria* species, *Fusarium* species, *Rhizomucor* species and *Trichoderma* species. The undesired enzymatic activities in such cultivation media are primarily enzymatic side activities that are produced naturally by the production strain for the desired polypeptide. However, in specific embodiments, the undesired side activity is derived from a fusion partner for the desired polypeptide.

The specification also discusses Ward et al., Biotechnol 8:435-440 ("Ward"), published in May 1990, which establishes that fusion proteins having glucoamylase activity were well known at

the time of the invention. Ward utilizes *Aspergillus niger* var. *awamori* to express a fusion protein, but also states that "[p]rochymosin cDNA has been expressed in other microbes, including *Escherichia coli*, *Saccharamyces cervisiae*, and *Yarrowia lipolytica*." Ward, page 435, col. 2, 3d paragraph. All of the foregoing facts point unmistakably to the conclusion that the materials for "providing a medium having a pH of 2.0 or higher that comprises chymosin activity and glucoamylase activity" were widely available in the art and in possession by Applicant when the application was filed. Moreover, the Office Action fails to set forth a reasonable basis for doubting the truth of what is stated in the specification. Accordingly, the rejection of claims 1, 5-6, 9-14, 16-18, 29-31, 35-36, 39, and 42-43 under 35 U.S.C. § 112, first paragraph, for lack of written description must be withdrawn.

Enablement -- 35 U.S.C. § 112, first paragraph

The Office Action rejects claims 1, 5-6, 9-14, 16-18, 29-31, 35-36, 39, and 42-43 under 35 U.S.C. § 112, first paragraph, for lack of enablement.

"In order to make a rejection, the examiner has the initial burden to establish a reasonable basis to question the enablement provided for the claimed invention." M.P.E.P. § 2164.04 (citing In re Wright, 999 F.2d 1557, 1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993)). "A specification disclosure which contains a teaching of the manner and process of making and using an invention in terms which correspond in scope to those used in describing and defining the subject matter sought to be patented must be taken as being in compliance with the enablement requirement of 35 U.S.C. 112, first paragraph, unless there is a reason to doubt the objective truth of the statements contained therein which must be relied on for enabling support . . . [I]t is incumbent upon the Patent Office, whenever a rejection on this basis is made, to explain why it doubts the truth or accuracy of any statement in a supporting disclosure and to back up assertions of its own with acceptable evidence or reasoning which is inconsistent with the contested statement. Otherwise, there would be no need for the applicant to go to the trouble and expense of supporting his presumptively accurate disclosure." M.P.E.P. 2164.04 (quoting In re Marzocchi, 439 F.2d 220, 224, 169 USPQ 367, 370 (CCPA 1971)).

The Office Action states the following "[w]hile one of skill in the art would have the ability to express a pro-chymosin-glucoamylase fusion protein using bacteria or yeast as an

expression host, introducing a heterologous glucoamylase activity into the medium of these microorganisms would not appear to be the 'best mode' for carrying out the invention, particularly as the specification describes glucoamylase activity as an 'undesired enzymatic activity.'" Office Action, page 11. As an initial matter, Examiner Steadman clarified during the interview that there was no assertion of failure to disclose best mode here and that the ground for invalidity was not what he was discussing. Applicant understands this comment as questioning why a person would want to make something having glucoamylase activity in the first place. In response, Ward teaches making a glucoamylase-chymosin fusion protein because it is secreted at higher efficiency relative to other chymosin expression vectors. See, e.g., Ward, Abstract.

Applicant agrees with the Examiner's statement that "one skilled in the art would have the ability to express a pro-chymosin-glucoamylase fusion protein using bacteria or yeast as an expression host." Office Action, page 11. Indeed, Ward, which was published fifteen years ago, teaches that "[p]rochymosin cDNA has been expressed in other microbes, including *Escherichia coli*, *Saccharamyces cervisiae*, and *Yarrowia lipolytica.*" Ward, page 435, col. 2, 3d paragraph. As discussed above, the Office Action also fails to consider the commercial availability of the starting materials disclosed in Example 3. The Office Action therefore fails to "explain why it doubts the truth or accuracy of any statement in a supporting disclosure and to back up assertions of its own with acceptable evidence or reasoning which is inconsistent with the contested statement." See M.P.E.P. § 2164.04, supra. The broad scope of evidence of enablement of record has been completely ignored in the statement of rejection, which begins on page 8 and ends on page 15 of the Office Action. Without consideration of all the disclosed examples, the rejection for enablement is fatally flawed and must be withdrawn. Accordingly, the rejection of claims 1, 5-6, 9-14, 16-18, 29-31, 35-36, 39, and 42-43 under 35 U.S.C. § 112, first paragraph, for lack of enablement must be withdrawn.

Obviousness -- 35 U.S.C. § 103

The Office Action rejects claims 1, 5-6, 9, 12-14, 16-18, 29-31, and 42-43 under 35 U.S.C. § 103 as being unpatentable over Ward in view of Larsen.

"To establish a prima facie case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the

knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations." Manual of Patent Examining Procedure § 2143.03 (8th ed., rev. 2, May 2004) (hereinafter "M.P.E.P."). "In relying upon the theory of inherency, the examiner must provide a basis in fact and/or technical reasoning to reasonably support the determination that the allegedly inherent characteristic necessarily flows from the teachings of the applied prior art." M.P.E.P. § 2112 (quoting Ex parte Levy, 17 USPQ2d 1461, 1464 (Bd. Pat. App. & Inter. 1990) (emphasis in original)). "The fact that a certain result or characteristic may occur or be present in the prior art is not sufficient to establish the inherency of that result or characteristic." Id. (citing In re Rijckaert, 9 F.3d 1531, 1534, 28 USPQ2d 1955, 1957 (Fed. Cir. 1993), which reversed rejection because inherency was based on what would result due to optimization of conditions, not what was necessarily present in the prior art).

Both Ward and Larsen are discussed in the specification. Ward is discussed at page 2, lines 19-23. Larsen is discussed at page 3, lines 19-21.

Ward teaches improved production of chymosin in *Aspergillus* by expression of a glucoamylase-chymosin fusion protein. See Ward, Title & Abstract. In particular, Ward teaches that the glucoamylase-chymosin fusion proteins can be secreted at higher efficiency compared to prochymosin. Ward, page 438, col. 1, last paragraph. Ward teaches that lowering the pH to 2 converts the fusion protein to chymosin and at least some pseudochymosin. Ward, page 439, col. 2, first paragraph. Ward teaches that "[p]resumably, this would eventually be further processed to mature chymosin under appropriate conditions." Ward, page 439, col. 2, first paragraph. Ward further teaches that "[p]seudochymosin is fairly stable at a pH below 3 or above 6 but is further processed to mature chymosin at pH 4.5." Ward, page 435, col. 1, first paragraph after the Abstract. Thus, Ward suggests raising the pH to 4.5 after activating the chymosin at a pH of 2.0 to convert any pseudochymosin to chymosin.

With respect to claim 1, the Office Action correctly acknowledges that Ward does not teach "practicing their method at a pH below 2.0." Office Action, page 18. In fact, claim 1 differs from Ward by requiring "subjecting said medium to a pH in the range of 1.0 to 1.99 for a period of time sufficient to inactivate at least 50% of said glucoamylase activity while

maintaining at least 75% of said chymosin activity." Ward teaches neither reducing the pH of activated chymosin below 2.0 or inactivating "at least 50% of said glucoamylase activity while maintaining at least 75% of said chymosin activity." In fact, Ward teaches against Applicant's invention of claim 1 because he suggests increasing the pH of the medium to 4.5 after chymosin activation at pH 2.0 to convert pseudochymosin to chymosin. Finally, Ward is not directed to solving the problem of unwanted glucoamylase activity (side activity), but is focused singularly on increasing secretion efficiency of chymosin. To overcome the deficiencies of Ward, the Office Action turns to Larsen.

Larsen teaches separation of milk clotting aspartic endopeptidases present in an extract of animal tissue using a one-step chromatography process that avoids the use of PEG and salt. See discussion of Larsen in the specification at page 3. Larsen teaches conversion of pre-enzymes into active endopeptidases at a pH ranging between 0.5 to 5.0 including 2.0 for a period of time ranging from 20-60 minutes. Larsen, page 10. Example 3 of Larsen reads, "The rennet extract was activated at pH 2" and example 6 reads: "An aqueous rennet extract of calf stomachs prepared essentially as described in Example 4 was activated at pH 2." Larsen, page 40, 46. Larsen does not mention the problem of glucoamylase side activity. Although Larsen teaches providing a medium having a pH of 2.0 or higher that comprises chymosin activity, i.e., the activation step, there is no subsequent step of reducing the pH after the chymosin is activated for any reason. Accordingly, there can be no step of inactivating 50% of an unwanted side activity while maintaining at least 75% of the chymosin activity in Larsen.

The Office Action concludes that "it would have been obvious to one of ordinary skill in the art to combine the teachings of Ward et al. and Larsen et al. to practice the method of Ward et al. using a pH as low as 0.5 in order to determine whether pH values lower than 2.0 increase the amount of cleaved fusion protein or increase the rate at which cleavage of the fusion protein occurs, particularly in view of the teaching of Ward et al. that cleavage of the fusion protein is 'favored at low pH'." Office Action, page 19. The Office Action further concludes that the claimed result of inactivating at least 50% of said glucoamylase activity while maintaining at least 75% of said chymosin activity would have been inherent in "practicing the method of Ward et al. at a pH as low as 0.5." Office Action, page 20.

First, the Office Action has failed to "provide a basis in fact and/or technical reasoning to reasonably support the determination that the allegedly inherent characteristic necessarily flows from the teachings of the applied prior art." As a result, the asserted combination does not teach every limitation of the claim. "To establish prima facie obviousness of a claimed invention, all the claim limitations must be taught or suggested by the prior art." M.P.E.P. § 2143.03 (citing In re Royka, 490 F.2d 981, 180 USPQ 580 (CCPA 1974)). Larsen, which the Office Action relies on for a teaching of pH below 2.0, actually teaches a range of pH from 0.5 to 5.0, 1.0 to 3.0, and 1.5 to 2.5. Larsen, page 10. Indeed, none of the pH ranges taught by Larsen fall completely within the claimed range of 1.0 to 1.99 and the only specific pH value taught by Larsen is a pH value of about 2.0 and for the same purpose as in Ward--to activate chymosin. As seen from the data in Fig. 1 and Examples in this application, the drastic reduction in glucoamylase activity occurs over a pH range that is not taught by Larsen and will not necessarily result from practicing the method of Larsen. Accordingly, the claimed feature of "subjecting said medium to a pH in the range of 1.0 to 1.99 for a period of time sufficient to inactivate at least 50% of said glucoamylase activity while maintaining at least 75% of said chymosin activity" is not inherent in the teachings of Larsen or Ward or their combination.

Second, the Office Action has failed to set forth a motivation for practicing Ward at a pH of below 2.0 for any reason, much less to "to inactivate at least 50% of said glucoamylase activity while maintaining at least 75% of said chymosin activity." Neither Ward nor Larsen teach that any specific results can be achieved by lowering the pH below 2.0 other than activation of chymosin, which they both teach occurs at a pH of 2.0. Although Ward states that chymosin activation is favored "at low pH," Ward, page. 20, bottom, a careful reading of Ward makes clear that "low pH" means a pH of 2. The only motivation offered in the Office Action for lowering the pH of Ward below 2.0 using the broader range teachings of Larsen is to see what happens--specifically, "to determine whether pH values lower than 2.0 increase the amount of cleaved fusion protein or increase the rate at which cleavage of the fusion protein occurs." Office Action, page 19. Such an "obvious to try" analysis is erroneous as a matter of law.

The Office Action cites In re Aller, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955) for the proposition that "it is not inventive to discover the optimum or workable ranges by routine experimentation." However, reducing the pH in Ward to below 2.0 after activating the

chymosin at pH of 2.0 "to inactivate at least 50% of said glucoamylase activity while maintaining at least 75% of said chymosin activity" involves more than mere optimization--it is an additional step that is nowhere suggested in the prior art of record. In fact, introducing such an additional step into Ward would be contrary to Ward's explicit disclosure suggesting the pH adjustment in his second step to a pH of 4.5. Finally, the use of an optimization rationale for finding inherency based on Ward and Larsen is ineffective because "[t]he fact that a certain result or characteristic may occur or be present in the prior art is not sufficient to establish the inherency of that result or characteristic." M.P.E.P. § 2112 (citing In re Rijckaert, 9 F.3d 1531, 1534, 28 USPQ2d 1955, 1957 (Fed. Cir. 1993), which reversed rejection because inherency was based on what would result due to optimization of conditions, not what was necessarily present in the prior art).

Claim 1 is thus unobvious in view of the combined teachings of Ward and Larsen. Claims 5-6, 9-14, 16-18, 29-31, 35-36, and 42 are likewise unobvious as they depend from and incorporate the limitations of claim 1. Applicant also submits that the dependent claims deserve separate patentability consideration because they introduce limitations not found in either Ward or Larsen. Accordingly, the rejection of claims 1, 5-6, 9-14, 16-18, 29-31, 35-36, and 42 under 35 U.S.C. § 103 must be withdrawn.

Applicant submits that this response addresses all of the issues raised in the Office Action and places the pending claims in condition for allowance. Should any issues remain to be discussed in this application, the undersigned may be reached by telephone. In the event any variance exists between the amount authorized to be charged to the Deposit Account and the Patent Office charges for reconsideration of this application, please charge or credit any difference to the undersigned's Deposit Account No. 50-0206.

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